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Effectiveness and safety of vancomycin powder injection locally applied in the prevention of prosthetic joint infection

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Prosthetic joint infection (PJI) is a rare but serious complication associated with considerable morbidity and financial burdens and other hardships for the individual. The available treatment options for PJI include both surgery and antimicrobial therapy. The surgical option includes debridement, antibiotics and implant retention (DAIR), that is usually recommended at initial stages, one stage or two stage revision arthroplasty at advanced stages. These treatments are expensive and time consuming and have around 11-30% failure rate. Therefore, there is an urgent need for an appropriate and affordable treatment strategy. Vancomycin serves as an active agent against the pathogens that have ability to cause potential damage to the wounds after surgery. In its powder form, it ensures adequate surgical site concentrations while minimizing the adverse effects caused by undetectable systemic distribution. Thus, we explored the effectiveness and safety of vancomycin powder injection locally applied in the prevention of prosthetic joint infection (PJI). A total of 90 inpatients who underwent total hip and knee arthroplasty from January 2018 to December 2019 were selected and randomly divided into control group (routine preventive antibiotic therapy) and treatment group (vancomycin applied based on the treatment of control group). The incidence of PJI and adverse reactions within 3 months after operation was observed. The changes in body temperature, neutrophil count, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) levels were recorded before operation and 1, 3 and 7 days after treatment. Ninety days after treatment, the incidence rate of PJI in treatment group (0.00) was significantly lower than that of control group (8.89%) (P <0.05). Within a short period of time (1 d and 3 d) after treatment, the body temperature, neutrophil count, IL-6 and hs-CRP levels were all lower in treatment group than those in control group (P <0.05). However, the above indices had no significant differences between the two groups at 1 week (7 d) after treatment (P >0.05). There were 3 cases (6.67%) and 2 cases (4.44%) of adverse reactions in treatment group and control group, respectively. The incidence rates of adverse reactions were similar (χ^2=0.212, P=0.645). Vancomycin powder injection locally applied can control the body temperature, and reduce the neutrophil count, IL-6 and hs-CRP levels within a short period of time after operation, which is superior to routine preventive antibiotic therapy. It can decrease the incidence rate of PJI after arthroplasty.

Keywords: C-reactive protein, Interlukin, Neutrophil, Total hip arthroplasty, Total knee arthroplasty

Worldwide, patients undergoing arthroplasty is no more uncommon. In the United States alone, there have been more than 3,41,000 cases of hip arthroplasty and 7,19,000 cases of knee arthroplasty[1]. Prosthetic joint infection (PJI) is the most common reason for the re-hospitalization of patients undergoing arthroplasty, and its annual incidence rate is about 5%[2]. In the United States, about 566 million dollars are spent on the re-hospitalization caused by PJI each year, which may exceed 1.6 billion dollars by 2020[3]. *Staphylococcus* is the most common pathogen causing PJI, and methicillin-resistant *Staphylococcus aureus* (MRSA)-induced infection limits the application of antibiotics. Local application of antibiotics can maximize the local antibiotic concentration at the wound while reducing the systemic drug concentration and avoiding adverse reactions, thereby creating a better environment for sterilization. In recent years, the effectiveness of vancomycin powders locally applied in reducing infections after spinal surgery has been widely assessed[4-6]. However, vancomycin has seldom been locally applied in the prevention of PJI hitherto. In this study, therefore, the incidence of infection and related adverse reactions was analyzed and compared among patients treated with vancomycin and routine regimen, aiming to provide evidence for the clinical prevention of PJI.

Materials and Methodology

Baseline clinical data

A total of 90 inpatients who underwent total hip arthroplasty (THA) and total knee arthroplasty (TKA)

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in our hospital from January 2018 to December 2019 were selected. Inclusion criteria: (i) Patients aged 60-80 years old; 2(iithose who needed unilateral THA and TKA; (iii) those not allergic to "cephalosporin" antibiotics and traditional Chinese medicine used in this study; (iv) those with good compliance and treated in strict accordance with the established therapeutic regimen; and (v) those who signed the informed consent. Exclusion criteria: (i) Patients complicated with other pathological fractures except that caused by osteoporosis; (ii) those complicated with fractures at other sites, such as fracture of femoral shaft; (iii) those who were complicated with severe medical diseases, and still could not receive operation after medical consultation and treatment; (iv) those who heavily drank recently or took other drugs affecting the research results, such as glucocorticoids; and (v) those who failed to cooperate in the study, such as patients with mental diseases. The patients enrolled were randomly divided into vancomycin group (treatment group, n=45) and routine regimen group (control group, n=45). In treatment group, there were 24 males and 21 females aged (67.89±5.48) years old on average. THA and TKA were performed for 30 cases and 15 cases, respectively, including 29 cases of unilateral arthroplasty and 16 cases of bilateral arthroplasty. In control group, there were 23 males and 22 females aged (68.02±5.35) years old on average. THA and TKA were performed for 29 cases and 16 cases, respectively, including 30 cases of unilateral arthroplasty and 15 cases of bilateral arthroplasty. There were no statistically significant differences in baseline clinical data between the two groups (P >0.05).

Methods

Routine preventive antibiotic therapy was used for all patients: 1 g of cefazolin was given at 0.5 h before operation, and 1 g was additionally given every 8 h after operation. For patients allergic to cefazolin, 0.6 g of clindamycin was given at 0.5 h before operation, and 0.6 g was additionally given every 8 h after operation. The antibiotic treatment lasted for 48 h in both groups. For treatment group, vancomycin powder injection was locally applied in addition to the routine preventive antibiotic program: 1 g of vancomycin powder injection was applied at the surgical incision of patients undergoing unilateral arthroplasty, while 1 g of vancomycin powder injection was applied on each side of the surgical incision of patients undergoing bilateral arthroplasty. Vancomycin powder injection was applied at the surgical incision as follows: 0.5 g of vancomycin powder injection was placed into the acetabular fossa. The joint was dislocated after mold trial of the femoral head, the mold head and femoral myelocavity file were taken out, and 0.5 g of vancomycin powder injection was placed into the medullary cavity.

Observation indices

The changes in body temperature, neutrophil count, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) levels were observed and recorded before operation and at 1, 3 and 7 d after treatment. The incidence of PJI and adverse reactions was observed.

Diagnostic criteria for PJI

The diagnostic criteria for PJI were developed based on the Alexander's diagnostic criteria: (i) Joint infection can be diagnosed if fistulas are found in the affected hip or knee during treatment, and the fistula is connected to the joint; and (ii) It can also be diagnosed in the case of the following two or more conditions: (a) Positive bacterial culture of joint fluid in the affected hip or knee or intraoperative tissue specimens detected in the Laboratory Department of our hospital, (b) a significant increase in the neutrophil count in intraoperative tissue specimens, and (c) the diagnosis is confirmed by clinical symptoms (systemic fever, joint pain, etc.), laboratory tests (blood routine, IL-6 and hs-CRP levels, etc.) and radiography (X-ray, CT or MRI).

Statistical analysis

All data were statistically analyzed by SPSS 23.0 software. The quantitative data were expressed as mean ± standard deviation and compared with the independent samples t test. The numerical data were represented as rate (%) and compared by the χ^2 test. P <0.05 was considered statistically significant.

Results

Incidence rates of PJI

At 90 d after treatment, the incidence rate of PJI in treatment group (0.00) was significantly lower than that in control group (8.89%) (P <0.05) (Table 1).

Table 1 — Incidence rates of PJI (n=45)

Group	Without infection	With infection	Infection rate (%)
Control	45	0	0.00
Treatment	41	4	8.89
χ^2			4.186
P			0.041

Table 2 — Changes in body temperature, neutrophil count, IL-6 and hs-CRP levels (n=45)

	Pre-operative	Postoperative 1st day	3rd day	7th day
Body temperature (°C)				
Control group	36.5±0.39	37.4±0.32	37.2±0.39	36.6±0.41
Treatment group	36.6±0.40	37.7±0.33	37.5±0.40	36.7±0.40
t	1.201	4.378	3.602	1.171
P	0.233	0.000	0.001	0.245
Neutrophil count ($\times10^9$/L)				
Control group	5.4±0.50	6.8±0.61	6.4±0.51	6.2±0.50
Treatment group	5.5±0.51	7.5±0.62	6.8±0.54	6.3±0.49
t	0.939	5.399	3.613	0.958
P	0.350	0.000	0.000	0.341
IL-6 (pg/mL)				
Control group	31.2±5.45	84.7±6.24	62.5±5.48	46.4±3.29
Treatment group	31.5±5.39	92.3±6.35	68.6±5.56	46.7±3.42
t	0.263	5.727	5.242	0.424
P	0.794	0.000	0.000	0.673
CRP (mg/L)				
Control group	9.0±1.2	37.8±3.43	28.3±3.28	19.0±2.14
Treatment group	8.9±1.1	47.8±4.35	36.4±3.19	19.2±2.11
t	0.412	12.109	11.876	0.446
P	0.681	0.000	0.000	0.656

Changes in body temperature, neutrophil count, IL-6 and hs-CRP levels

Within a short period of time (1 and 3 d) after treatment, the body temperature, neutrophil count, IL-6 and hs-CRP levels were all lower in treatment group than those in control group (P <0.05). However, the above indices had no statistically significant differences between the two groups at one week (7 d) after treatment (P >0.05) (Table 2).

Postoperative adverse reactions

There were 3 cases (6.67%) and 2 cases (4.44%) of adverse reactions in treatment group and control group, respectively. It can be seen that the incidence rate of adverse reactions had no statistically significant difference between the two groups (χ^2=0.212, P=0.645). Specifically, treatment group had 1 case of rash, 1 case of hemocytopenia and one case of renal dysfunction, while control group had two cases of rash. All adverse reactions were improved through clinical treatment.

Discussion

With the maturity of manufacturing technique of artificial joint prosthesis and the improvement and development of surgery and anesthesiology, artificial joint replacement has been increasingly popularized in the treatment of severe hip and knee joint diseases, but postoperative PJI has always plagued people. The incidence rate of PJI was up to 9.1% as early as the 1980s[7]. With the recent medical advancements, the incidence rate of PJI has been controlled at 0.2-4% currently[8,9]. PJI will bring mental and economic burden to patients and their families, and it has fatal consequences if not treated properly[3]. Coagulase-negative Staphylococcus and Staphylococcus aureus are the main pathogens for PJI[10], but other rare pathogen infections can also occur sometimes, such as PJI caused by *Fusobacterium nucleatum*[11] and non-*Candida albicans*[12] reported recently. With the application of antibiotics, PJI caused by drug-resistant strains have increased, and some susceptible bacteria even have multi-drug resistance, so that there are fewer and fewer available antibiotics[13]. These pathogens cause infection around the prosthesis mainly through two ways[14], *i.e.* direct invasion and blood-borne infection. Direct pollution mainly results from the insufficient sterilization of surgical instruments, implanted prosthesis and surgical sites. In recent years, susceptibility factors for prosthesis have been studied in China and foreign countries. For example, it is pointed out in the AAOS Guidelines[8] that the absolute risk factors for PJI after arthroplasty include epidermal infection, obesity and operation time >2.5 h, and its relative risk factors include a history of bacteremia and fungemia within 1 year, skin diseases, a history of MRSA within 3 years, and acute infection at other sites. Postoperative atrial fibrillation, myocardial infarction and other medical diseases are also risk factors[15]. Recently, the cases of blood-borne group B streptococcal (GBS) PJI caused by sashimi dish (snakehead fish and Asian blackfish) have also been reported abroad. Therefore, it is recommended that "sashimi dish" be listed as a risk factor for PJI.

Preventing the occurrence of perioperative infection can not only insulate patients from the risk of secondary operation, but also save the resulting medical expenses. Ischemia or hematoma often occurs at the postoperative wound, both of which are not conducive to the absorption of antibiotics[16]. Therefore, antibiotics locally applied in infection prevention, characterized by higher drug concentration and lower systemic toxicity, are favoured by orthopedic surgeons. It has been confirmed that vancomycin powder locally applied to prevent postoperative infection has better clinical efficacy in spinal surgery in adults or children. Sweet *et al.*[17] conducted a retrospective analysis of 1,732 patients undergoing thoracolumbar spinal fusion, and found that vancomycin powder locally applied could reduce the

incidence rate of infection from 2.6 to 0.2%. In the research group, 2 g of vancomycin was applied, of which 1 g was mixed with bone grafts, and the other 1 g was evenly sprinkled on the deep tissues and wound surface during the closure of surgical incision. After the follow-up period of 2.5 years on average, no adverse reactions associated with vancomycin powder locally applied occurred. Qadir *et al.*[18] reported that vancomycin powder locally applied could greatly reduce the incidence rate of infection from 13% to 0 in patients with spinal trauma after posterior spinal fusion surgery. Moreover, the research results of Zhu *et al.*[19] manifested that the incidence rate of infection in patients undergoing posterior cervical fusion surgery declined from 10.9% to 2.5% after local application of vancomycin. However, there are few reports about patients undergoing artificial joint replacement currently. Antibiotic-laden bone cements used to be the main local application method of antibiotics for patients receiving arthroplasty, but their usage has been reduced with the application of bioprosthesis. In this study, it was found that vancomycin powder locally applied could lower the incidence of PJI after arthroplasty. However, whether vancomycin locally applied will lead to allergic reactions, acute renal failure and other adverse reactions still needs attention.

Gans *et al.*[20] retrospectively analyzed the renal function of 1,828 patients undergoing hip and knee arthroplasty, and the results showed that the risk of acute renal failure significantly rose under the combination of cefazolin and vancomycin locally applied compared with that under the single application of cefazolin. In this study, there was no statistically significant difference in the incidence rate of adverse reactions between vancomycin regimen and ordinary regimen. Vancomycin is a soluble molecule, but its clearance rate and precipitation characteristics in joint fluid have not been reported yet. Moreover, the effect of vancomycin locally applied on prosthetic joint wear requires special attention. High-quality research remains to be done to verify whether vancomycin powder will become a part of the prosthetic joint in a confined space of knee or hip joints, ultimately leading to abnormal wear and failure of prosthetic joint implantation.

At present, PJI is diagnosed based on clinical symptoms combined with pathogen culture of surrounding tissues of prosthesis[15]. However, clinical prevention is more important than treatment. Therefore, the physical condition can be comprehensively analyzed through monitoring body temperature, hemogram and hs-CRP, so as to guide clinicians in postoperative preventive medication. Monitoring postoperative body temperature can detect the presence or absence of infection in advance. Body temperature often tends to be higher within 72 h after operation, but the high body temperature after 72 h is often considered to be caused by infection[21]. Neutrophil count is a commonly used index determining whether infectious diseases occur, and it is often detected *via* postoperative blood routine review under normal conditions. Hs-CRP exerts an immunomodulatory effect in the body, and its content will rise in the case of obvious inflammatory response. In this study, vancomycin powder locally applied could control the body temperature, and reduce the neutrophil count, IL-6 and hs-CRP levels within a short period of time after operation, demonstrating that vancomycin powder locally applied can inhibit some inflammatory factors and control the infection trend.

Conclusion

In the above study, vancomycin powder injection locally applied has been demonstrated to control the body temperature, and reduce the neutrophil count, IL-6 and hs-CRP levels within a short period of time after surgery, which is superior to routine preventive antibiotic therapy. It can decrease the incidence rate of PJI after arthroplasty, which is relatively safe. However, its effectiveness and safety remain to be verified through more specific studies. Whether vancomycin locally applied will increase the drug-resistant bacterial infection and its effect on joint wear also need further research'

Conflict of interest

Authors declare no competing interests.

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